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MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 SEARS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,938	YAN ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84,85,87-91,96-108 and 110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84, 85, 87-91, 96-108 and 110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 84, 85, 87-91, 96-108 and 110 are pending in the instant application and are the subject of the Office Action below.

Any rejections or objections not reiterated in the instant Office Action are considered withdrawn.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 84, 85, 87-91, 96-108 and 110 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is maintained in modified form. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the claims do not have written description support for the full breadth of the claims. Although it appears that Applicants have support for the claim breadth where P_2 is N; P_1 is Y, L or F; $P_{1'}$ is E, A or D; and $P_{2'}$ is V, these teachings do not support the additional claim breadth that is currently claimed (see the specification, page 19, paragraph 2).

Applicants allege that the amended claims have support for the embodiment where the substrate of P_2P_1-$P_1'P_2'$ is NF-AA. Applicants point to support in the specification where in some instances a peptide substrate had N at position P_2, other peptides where P_1 was F, in some instances where $P_{1'}$ was E, and certain other peptide substrates had A for $P_{2'}$ (Reply, page 8, paragraph 3). Applicants also provide their summary of the art that the Examiner utilizes to show the unpredictable nature of the art and how it shows that Applicants' were not in possession of the claimed subsequence NF-AA. Applicants appear to suggest how the fact that

the references being published after the filing date is less than proper for demonstrating inadequate written description.

The Examiner disagrees. First, Applicants support in the specification is, at best, a hind-sight selection of a particular species from a genus or sub-genus. Applicants never disclose the specific sequence that is now being claimed, namely, NF-EA, either by a particular working example or by means of a prophetic example. This pattern of facts is similar to the case of *In re Ruschig*, 154 USPQ 118 (CCPA 19667), where the court determined that certain compounds may not be handpicked from broadly devised genus. In particular, the court stated:

> "[i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is of no help in finding a trail or in finding one's way through the woods where the trails have disappeared—or have not yet been made, which is more like the case here—to be confronted simply by a large number of unmarked trees. We are looking for blaze marks which single out particular trees. We see none."

Id., 154 USPQ at 122.

See also *Purdue Pharma L.P. v. Faulding, Inc.*, 56 USPQ2d 1481 (Fed. Cir. 2000), where the court also determined that later claiming a particular species from a broader disclosure without guidance or "blazemarks" was unsupported by 35 U.S.C. § 112, first paragraph.

Second, Applicants' piecemeal analysis of the art does not overcome the objective consideration that one of ordinary skill in the art would develop regarding the art as a whole. Namely, that the art is largely unpredictable for one to rely on the methods suggested by Applicants based on a few species to select either other species and expect the selected species to have the same activity.

Third, it is not improper to rely on post-filing art to demonstrate the unpredictability of art at the time the invention was filed. If anything, the post-filing art concurs what those of skill in the art were thinking at the time of invention (*i.e.*, certain issues were still not resolved or did not overcome the unpredictability that results in undue experimentation).

Accordingly, the rejection is proper and is therefore maintained.

Reiterated Rejection:

The written description requirement is distinct from the enablement requirement; this was first pointed out by the court in *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), and

clarified in *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). The issue of whether the claimed subject matter is adequately supported/described by the specification, is a question of *fact*. *Id*. at 1563, 19 USPQ2d at 1116.

When considering whether the claimed subject matter complies with the written description requirement, Applicants' disclosure should be read in light of the knowledge possessed by those skilled in the art.

> "[T]he disclosure in question must be read in light of the knowledge possessed by those skilled in the art, and that knowledge can be established by affidavits of fact composed by an expert, and by referencing to patents and publications available to the public…"

In re Lange, 644 F.2d 856, 863, 209 USPQ 288, 294. *See also, In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Applicants enjoy the presumption that their patent application is valid and all statements contained therein are accurate; it is the PTO's burden to demonstrate why any of Applicants claims should be rejected or why any of Applicant's statements should be doubted.

> "it is incumbent upon the Patent Office, whenever a rejection… is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370. If successful in presenting such evidence and argument, the burden then shifts to the Applicant to provide evidence that would convince one to the contrary.

The Invention in General

A component of Applicants' invention is directed to a method for screening inhibitors of an enzyme (class of enzyme) involved in the progression of Alzheimer's disease (AD). Applicants provide a clear and succinct background of the invention by detailing certain biochemical pathways in the formation of the plaques responsible for AD. An origin of these plaques is the amyloid protein precursor (APP), which when first processed by an enzyme

having β-secretase activity, followed by an enzyme having γ-secretase activity, causes the formation of a 40/42 amino acid peptide plaque know as Aβ.

Accordingly, the development of methods for identifying compounds that might one day serve as potential β-secretase inhibitors are undoubtedly needed by the biomedical community in order to accelerate the development of AD drug candidates. As Applicants suggest, such a demand would benefit from the identification of a substrate that is more sensitive to the activity of β-secretase for use in an assay in identifying and characterizing potential inhibitors/drug candidates.

The Claimed Invention

The claimed invention (*e.g.*, claim 84) is broadly directed to a method for assaying for a modulator of β-secretase activity comprising contacting: (i) a peptide having β-secretase activity, with (ii) a peptide/substrate of the generic formula P_2P_1-P_1'P_2', wherein the amino acid "P" values are defined, but excluding certain peptides identified by SEQ ID NO, and measuring the activity in the presence and absence of a potential inhibitor compound.

Certain narrower embodiments of the claimed invention are presented in various dependent claims. Some of these claims further limit the various values for certain amino acid positions in the substrate sequence; other claims limit certain other aspects, including but not limited to the claimed labels, the length of the substrate, the presence of a quenching moiety, the polypeptide with the β-secretase activity, and assay milieu.

The Supporting Disclosure

Applicants' supporting disclosure contains numerous embodiments of the invention. Pages 3 through 5 list a number of different chemical genera of a peptide fragment comprising various groups of amino acids that have a scissile bond when reacted with a protein having β-secretase activity. For example, on page 3, the peptide fragment is defined by the genus P_2P_1-P_1'P_2', wherein P_2 is defined as a charged amino acid, a polar amino acid or an aliphatic amino acid but is not an aromatic amino acid, P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid; P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid; and P_2' is an uncharged

aliphatic polar amino acid or an aromatic amino acid but not a charged amino acid; wherein the peptide is cleaved between P_1 and P_1' by two certain human aspartyl proteases, and has certain other provisos.

Certain other embodiments further limit an aspect of the invention by describing the peptide fragments as certain sequence encoded by $P_4P_3P_2P_1$-$P_1'P_2'P_3'$, and list the possible amino acids that could by used at the corresponding P values. Applicants provide some guidance with respect to the preferred P values, and list those values on page 5. On page 6, Applicants describe particular sequences that are preferred peptides of the present invention by SEQ ID NO.

The disclosure describes a number of substrates encompassed by the claimed chemical genus that produce β-secretase activity, and conveniently groups these substrates by sequence similarity to illustrate certain trends or correlations (Tables 2-5, and description thereof). Following Table 3 on pages 21-23, the disclosure describes the particular substitutions and the resulting effects on activity (objective statements; not an explanation of the physicochemical properties as it relates to the enzyme system). The discussion following Table 5 on pages 25 and 26 is similar. The disclosure does, however, indicate on page 26 that extension of the N-terminal region of a particular peptide fragment is expected to enhance activity.

Regarding the claim breadth that the Examiner has acknowledged as supported, this support can be found, in-part, in the specification, page 19, paragraph 2, as well as certain tables in the specification illustrating activity for some of the species within the genus.

On pages 28 and 29, the disclosure describes the amino acids by their well-known characteristics and explains hydropathic indexing. In particular, the specification states:

> "It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of a resultant protein or peptide, which in turn defines the interaction of that protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics (Kyte & Doolittle, *J. Mol. Biol.*, 157(1):105-132, 1982, incorporated herein by reference). Generally, amino acids may be substituted by other amino acids that have a similar hydropathic index or score and still result in a protein with similar biological activity *i.e.*, still obtain a biological functionally equivalent protein or peptide. In the context of the peptides of the present invention, a biologically functionally equivalent protein or peptide will be one which is still cleaved by β-secretase at a rate exceeding

> the rate of cleavage of a nature [*sic*] APP peptide comprising SEQ ID NO: 20."

Applicants' disclosure, page 29, lines 6-18.

Table 6 lists Applicants exemplary amino acids that they consider to be useful at the positions P_4, P_3, P_2, P_1, P_1', P_2', P_3' and P_4'. It appears that the selection of these amino acids is based, in-part, on certain working examples (*i.e.*, tested peptide fragments having β-secretase activity), amino acids that are listed as equivalents to the working examples based on the hydropathic index, and possibly certain prophetic examples as listed on pages 30 and 31. It further appears that the combination of individual amino acids at each of the P values that form the claimed P_2P_1-P_1'P_2' peptide fragment are independently selected.

Additionally, the description discloses a number of other embodiments relevant to Applicants' invention, such as labels, fusion proteins, detection schemes, transgenic animals, certain laboratory preparation techniques, etc.

The State of the Art

A number of reference are relied upon as factual support in challenging certain statements made in the instant application and as a basis for rejecting the claims for lacking written description. For example, Gruninger-Leitch *et al.* ("Leitch"), *J. Biol. Chem. 277(7)*:4687-4693 (**2002**); Majer *et al.* ("Majer"), *Protein Science 6*:1458-1466 (**1997**); Sauder *et al.* ("Sauder"), *J. Mol. Biol. 300*:241-248 (**2000**); Shi *et al.* ("Shi"), *J. Alzheimer's Disease 7*:139-148 (**2005**); and Tomasselli *et al.* ("Tomasselli"), *J. Neurochemistry 84*:1006-1017 (**2003**); taken together, suggest that Applicants were not in possession of the claimed invention at the date of filing, and further, have not provided such sufficient description to support the invention as is broadly claimed. Specifically, the art as a whole provides sufficient evidence that demonstrates that Applicants' particular P_2P_1-P_1'P_2' species, taken in combination with their supporting disclosure, does not support the breadth of the claimed P_2P_1-P_1'P_2' genus.

Leitch discloses a comparison study between certain proteases including BACE, BACE2, cathepsin D and E, napsin A, pepsin and rennin, and teaches that BACE presents itself as an ideal target for AD treatment. In particular, Leitch teaches the specificity and activity of a number substrates that are cleavable by BACE in comparison to other proteases. Certain factors

identified in Leitch's teachings would suggest that Applicants' claimed genus is unsupported by their disclosure include the following factors: i) the effects of, and importance, of amino acids further from the scissile bond of the substrate, such as P_4, P_3, $P_{3'}$ and $P_{4'}$; ii) the length of the substrate required for cleavage by the BACE enzyme; and iii) certain *in vitro* and *in vivo* differences in activity, wherein any single factor may or may not be coupled to any other factor(s). Table 1 illustrates the effects of certain substrate mutations compared to the Swedish type APP substrate. A single amino acid mutation at P1' of the Swedish mutant APP β-cleavage site (NL-D → NL-A), results in an 84% drop in activity. Even more surprisingly, the P4K substrate which differs from the Swedish mutant APP β-cleavage site (NL-D) by a single amino acid at P_4, yet retains the same P_2P_1-$P_{1'}P_{2'}$ sequence, results in a 50-fold drop in activity (Table 1 on page 4689). These mutations and effects are relevant to the breadth and subject matter of Applicants' claims, and do not appear to be remedied by the art or Applicants' disclosure.

Similar to Applicants' approach (see pages 20-30 of the instant application), Leitch progressively optimizes certain substrates based on observed preferences in BACE substrates (pages 4690-4691). Although Applicants have optimized their sequences based on insulin and ubiquitin, such studies and a general reference to the hydropathic indexing of substrates does little to provide a structure-activity nexus for linking the broad array of species to the relatively large claimed genus. Leitch demonstrates a number of amino acids substitutions for certain positions within the cleavable peptide substrate, and reveals that certain amino acid combinations appear to be interdependent.[1] Leitch also teaches that the *in vivo* and *in vitro* differences can affect activities, possibly due to an orientation effect and the cell lumen (page 4692), and can be further complicated by the size of the substrate (page 4693).

Given the fact that the amino acid substitution effects are not necessarily additive, and that drastic effects in activity can be observed by changing amino acids either in the P_2P_1-$P_{1'}P_{2'}$ region, support for Applicants' genus is reasonably challenged by the teaching of Leitch. As a result of each of these factors, considered independently or as having a cumulative effect on the substrate/enzyme relationship, one of ordinary skill in the art would doubt that Applicants had adequately described the invention as broadly claimed.

Tomasselli also reports experimental findings that demonstrate that the claimed genus is not supported by the disclosed species because of amino acid interdependence and *in vitro* and *in vivo* differences in activity:

> "Enzyme subsites are interdependent and occupancy of a subsite by two 'well tolerated', but different amino acids, may differentially influence the amino acid preferences at the other subsites."

Tomasselli at page 1014, column 1; and again regarding the interdependence of amino acids:

> "Our findings indicate that amino acid preference at a specific site has to be regarded in the context of the peptide sequence rather than of maximal statistical occurrence of that amino acid at that specific position in the substrate. *A P1 Leu may be highly preferred in a library of peptide substrates, but Tyr is optimal at this position in our best substrate because of its interdependence upon its neighboring P-site substituents*. We have produced an optimal BACE1 substrate by systematic changes in individual P-sites considered globally with respect to the overall sequence, and by N-terminal extension of the peptides with the naturally occurring APP sequence."

Id. at page 1014, column 2 (emphasis added). Regarding Tomasselli's "systematic" approach, however, neither Applicants nor Tomasselli provide sufficient description to link all of the claimed species to the genus. Instead, one of ordinary skill in the art would consider the approaches of Leitch and Turner to be "systematically" different, but still systematic. For example, Shi discloses a BACE substrate identified by a library approach that is about 3-4 fold scissile than that disclosed by Tomasselli (Shi at page 141, column 2). Although certain approaches may be better served for identifying a few particular species, Applicants' and Tomasselli's approaches do not sufficiently describe the breadth of the genus as claimed.

Majer discloses a series of compounds produced through a systematic approach for optimizing inhibitor polypeptides to cathepsin D, an aspartic protease. Similar to optimizing BACE substrates with a scissile bond, a number of factors are important in substrate/inhibitor optimization, including but not limited to, hydropathy, orientation of the amino acid side chains, backbone configuration, hydrogen bonding, side chain length, and a number of subsite considerations, such as steric interactions, solvation, etc. Majer also teaches that there are

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[1] Leitch teaches that "the hydroxylamino acids Thr and Ser were found at position P2 only in combination with Ser

additional important considerations besides the P_2P_1-$P_1'P_2'$ amino acid residues (pages 1458-1465), and that amino acid substitutions are not necessarily additive (page 1462).

Many of the claimed amino acid substitutions do not necessarily follow from any disclosure, or the corresponding systematic approaches. One sequence that only differs from Applicants' most active substrate (SY-EV) is the sequence GY-EV as disclosed in Sauder (see Figure 4 on page 246, and description thereof on page 245), however, this sequence has drastically reduced in activity in comparison. Based on the hydropathic index, the single value difference between S → G is –0.4 (see page 110 of Kyte and Doolittle, *J. Mol. Biol. 157(1)*:105-132 (**1982**)). Vassar discloses that a substitution of a single amino acid to P1 of the APPwt (M → V), results in elimination of the scissile bond. Although the difference in going from M → V has a single position value difference in the hydropathic index of 2.3, the wt to Sweedish mutation has a hydropathic difference of comparable magnitude at 2.0 at P1 (Kyte at page 110).

P_2P_1-$P_1'P_2'$ Sequence	***Description***
KM-DA	APPwt
NL-DA	Swedish mutant with high increase in activity
KV-DA	lacks activity
GY-EV	low activity; the wt β'-secretase site
SY-EV	Applicants' most active sequence fragment
NF-EV	Shi's most active sequence fragment

However, it is not truly clear from Applicants' or any other "systematic" approach, or the teachings in the art, what effects certain amino acid substitutions will have on a substrate, even if the substitution is sometimes preferred for one particular substrate, or by relying on hydropathic indexing.

None of these approaches provide additional claim scope beyond the peptide substrates where P_2 is N; P_1 is Y, L or F; P_1' is E, A or D; and P_2' is V. See *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1905 (Fed. Cir. 1995), where the court noted that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species or subgenus of a genus because it would not reasonably lead those skilled in the art to any particular species. See

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at P1'."

also *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004), where a limited number of species does not necessarily provide written description support to a broader genus.

Accordingly, for at least these reasons, Applicants have not adequately described the invention for the breadth that is claimed. It thus appears that Applicants were not in possession of the claimed invention at the time the application was filed, the structure-function relationship between the protease and the scissile substrates have not been adequately set forth, and that Applicants' species do not support the claimed genus.

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should

Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Primary Examiner, Art Unit 1639